Statistical inference in variance components models for biomedical applications

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Chapter 5

The consequences of family structures in LifeLines cohort study for BMI mediated health related quality of life score

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Abstract

LifeLines is a three generation cohort study investigating the biological, behavioral and environmental determinants of healthy ageing. It is important to understand to what extent the family structure (correlation between family members) influences the associations between determinants and health outcomes. Therefore, the goal of this study is to investigate the impact of relatedness in a family on the association of body bass index (BMI) mediated health related quality of life (HRQoL) scores. Two forms of relatedness are considered. One form is based on shared environmental factors, and thus we have defined family as a group of individuals sharing the same environment. Another form of relatedness is based on heredity and thus, the fractional relatedness of founders and nonfounders are imposed and incorporated. HRQoL scores consist of mental and physical components. This study also aims to estimate the contribution of variances in outcomes due to shared environment and genetics. The effect of BMI is studied on both outcomes, in four models. One model does not account for relatedness, whereas others do account. The fixed effects of BMI are adjusted for covariates age and gender in all models.

We study LifeLines data issued in 2013. The data for analysis consists of 92892 participants from which we reconstructed 60765 families. About 55% of the LifeLines participants have at least one family member who also participate in LifeLines. Results show that the association between BMI on mental and physical components of HRQoL scores (along with standard errors) do not change with and without accounting for relatedness in a family. In variation of physical component score, 12-14% is determined by genetics and 3-5% by shared environment. In variation of mental component score, 16-18% is determined by shared environment. Thus, if one is interested to assess the contribution of various factors, then the variance components models should be considered which do account for family structure.

Keywords: Body mass index; Mental component of health related quality of life score; Physical component of health related quality of life score; Variance components models; Fractional relatedness; Heritability and its confidence interval.

5.1 Introduction

5.1.1 BMI and Health related quality of Life

Excessive weight, and especially obesity, is a major public health concern in the western world. Around two third of the adult population in the United States and at least half of the population of many European countries are currently overweight or obese (Wang et al., 2008, Berghöfer et al., 2008, Flegal et al., 2010). In the Netherlands, the prevalence of overweight is 48.3% (Volksgezondheid, 2012). As for obese, they are 12.7% of the total Dutch population. It is known that obesity - defined as a BMI of 30 or more - is a major risk factor for many chronic diseases, such as hypertension, stroke, coronary heart disease, diabetes and arthritis and overall mortality (Flegal et al., 2013, Prospective Studies Collaboration et al., 2009). Furthermore, increased BMI has also been shown to be associated with reduced physical HRQoL (Ul-Haq et al., 2012, 2013). However, evidence on the relationship between BMI and mental HRQoL is inconclusive. Some studies found that BMI is associated with poor mental health (Baumeister and Härter, 2007, Ohayon, 2007, Petry et al., 2008), whereas others did not found this negative relation (Crisp and McGuiness, 1976, Palinkas et al., 1996, Petry et al., 2008, Goldney et al., 2009). Ul-Haq et al. (2014) also investigated whether the association between BMI and mental health among Scottish adult population (n=37272), was moderated by age and sex. In contrast to the above mentioned studies, Ul-Haq et al. (2014) used the full spectrum of BMI and adjusted for potential confounders and found that only young obese women ($<$45 years of age with BMI $>$ 29.9 kg/m2) had significantly poorer mental health. Furthermore, being underweight was associated with poor mental health among women of all ages, but not men.

5.1.2 Background on LifeLines

LifeLines is a large population-based cohort study and biobank investigating the biological, behavioral and environmental determinants of healthy ageing among 167,729 inhabitants from the northern part of the Netherlands. The cohort profile of the LifeLines study has been described elsewhere (Scholtens et al., 2014). Briefly, the participant recruitment took place between 2006-2013. A random sample of persons aged between 25 and 50 years were invited by their general practitioners. Subsequently, family members (i.e. parents, partner, children)

were invited to participate, resulting in a three generation study (Stolk et al., 2008). In addition, participants could also register themselves via the LifeLines website. LifeLines adopted a three generation study design to disentangle the genetic, lifestyle and environmental contributions to the development of chronic diseases and study the between-generation similarities and identify the preclinical stages of ageing at an early age (Stolk et al., 2008). Baseline data were collected from 167,729 participants, of ages from 6 months to 93 years. Follow-up is planned for at least 30 years, with questionnaires administered every 1.5 years, and a physical examination scheduled every five years. The physical examination, including anthropometry, lung function, blood pressure, electro cardiogram (ECG) and cognition tests is conducted at one of the LifeLines research site. In addition, fasting blood and 24-hour urine samples are collected from all participants. A comprehensive questionnaire on history of (chronic) diseases, health related quality of life, lifestyle (physical activity, alcohol use, diet, smoking status), individual socioeconomic status (income and education level), psychosocial stress, work (profession, working hours), psychosocial characteristics, and medication use is completed at home. A comprehensive and detailed overview of the available data is presented in the online LifeLines Data Catalogue (www.lifelines.net).

5.1.3 Motivation and goal

Correlations between participants within the same family (for example, grandparent-grandchild, parent-child, sibling-sibling) in LifeLines was a motivation to incorporate these correlations in the model. We set two goals in our paper. One goal is to study the effect of BMI on mental and physical components of HRQoL scores with and without accounting for relatedness in a family. Another goal is to assess the contribution of shared environmental and genetic components in the variance of physical and mental components of HRQoL scores. LifeLines allows to model the relatedness in a larger and more complex families than in families with four to six members having a particular type of relatedness of the same size (e.g. twin-pairs, sibling-pairs with spouses), as mostly demonstrated by others (Pawitan et al., 2004, Noh et al., 2006, Yip et al., 2008, Rabe-Hesketh et al., 2008, Lichtenstein et al., 2009). For example, Pawitan et al. (2004), Noh et al. (2006) included pairs of families where the mothers are full sisters and the fathers

are unrelated men and used the variance components models to study the outcome pre-eclampsia. Their study also included brother-brother and brother-sister sibling-pairs with their spouses. Rabe-Hesketh et al. (2008) applied proposed reparametrization on twin data and nuclear families of trios including mother, father and a child. Yip et al. (2008) studied families with five members: for paternal half-siblings these were three parents (one father and two mothers) and the first known half-sibling. Lichtenstein et al. (2009) analyzed families involving six members with one effected proband and five unaffected relatives. This study included nuclear families as well as families with paternal and maternal half-siblings. Limitations of other studies related to sample sizes and particular type of family relatedness are potentially overcome by constructing and analyzing extended families in LifeLines. Subsequently, the components of interest such as genetic and shared environmental can be separated with higher precision compared to other studies.

Not only the variance components due to specific factors are of interests, but also the relative contribution of these variances in the total variance of the outcome. Related to this is the concept of heritability. The concept of heritability took its origin from Fisher (1919) and Wright (1920) and was formalized by Lush (1940). Extensive review on the concept and misconceptions of heritability is given by Visscher et al. (2008). In Section 5.2.5 we provide the definitions of both, broad and narrow sense heritabilities in the context of our models. We also briefly introduce the beta-approach (Demetrashvili et al., 2014) to construct the confidence interval for heritability. The beta-approach has been successfully applied to construct the confidence intervals for ratios of sums of variance components in linear and nonlinear mixed effects models (Demetrashvili et al., 2014, Demetrashvili and Van den Heuvel, 2015). This approach will use the first and second moments of the heritability estimate in combination with a beta distribution.

In Section 5.2 we provide background on reconstruction of families and outcome measures. Then we describe models, motivation of their use and selection criteria. In Section 5.3 we provide the descriptive statistics and results of modelling for LifeLines study.

5.2 Methods

5.2.1 Family reconstruction

LifeLines participants provide information about participation of their parents, spouses and children in LifeLines. This information is relevant to disentangle the genetic and shared environmental variances. In biometrical genetics, the coefficient of relatedness or genetic correlation for two individuals is defined as the expected proportion of genes of the two individuals that are identity-by-decent (Sham, 1998, p.208). Another concept of biometrical genetics which is used in this work is a founder. Individuals without ancestors in the family are called founders, whereas the remaining ones are called nonfounders (Almgren et al., 2003, p.10). Founders in our study population are assumed unrelated.

Considering information declared by LifeLines participants, we define family as a group of individuals sharing the same environmental factors. Families may be called extended because they may include following related individuals of a proband: parents, spouse(s), children (including from previous marriages), children-in-law, siblings with their spouses, etc. If one of the two participants declares being in a stated relationship (e.g. spouse-spouse), then we consider them to be in such a relationship. Information on spouses and children from previous marriages is also available in LifeLines. If one of the spouses does not mention about a particular child and this child does not mention about that "potential parent", then we assume that this "parent-child" pair is not in a genetic relationship.

5.2.2 Outcome measures

We used a subsample of the baseline LifeLines cohort study (data release 2013_02) which includes 95433 participants. HRQoL was measured using the Dutch version of the RAND-36 (Van der Zee and Sanderman, 1993, Van der Zee et al., 1996, Hays and Morales, 2001). HRQoL refers to how health impacts on an individual's ability to function and his or her perceived well-being in physical, mental and social domains of life. The RAND-36 consisted of 36 items measuring eight health concepts, i.e. physical functioning, role limitations caused by physical health problems, bodily pain, general health perceptions, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue. The first four reflect the physical

health and the last four reflect the mental health. The scales of these eight concepts are combined into two summary measures of HRQoL, the physical component score (PCS) and the mental component score (MCS). The scoring algorithm for a PCS includes positive weights for the physical functioning, role-physical, bodily pain, general health and energy scales, and negative weights for the role-emotional, social functioning, and emotional well-being scales (Ware et al., 1994). The scoring algorithm for a MCS includes positive weights for the role-emotional, social functioning, emotional well-being and energy scales, and negative weights for the physical functioning, role-physical, bodily pain and general health scales (Ware et al., 1994). Thus, high mental health scores tend to drive the PCS down and high physical health scores tend to drive the MCS scores down. PCS and MCS are between 0-100% and higher scores correspond with better quality of life.

5.2.3 Statistical models

We compare four models to examine whether the effect of BMI differs without and with accounting for family structure. These models are: M_0-multiple linear regression model, M_1-variance components model for the family which alternatively is a mixed effects model with random intercept for the family, M_2-variance components model for the founders which is also a mixed effects model with random slopes for founders within a family. The fourth model, M_3 is a combination of the last two models. Thus, M_3 is the variance components model for the family and founders which alternatively is a mixed effects model with random intercept for the family and random slopes for founders. Suppose for the ith family n_i members have been observed, $i = 1, 2, \ldots, I$, $j = 1, 2, \ldots, n_i$ with I be the total number of families and $N = \sum_{i=1}^{I} n_i$ be the total number of observations. Let y_{ij} is response for jth member of ith family. Multiple regression model M_0 can be written:

$$\begin{aligned} y_{ij} &= \mathbf{x}_{ij}^T \beta + \epsilon_{ij} \\ \epsilon_{ij} &\overset{iid}{\sim} N(0, \sigma_R^2), \end{aligned} \tag{5.1}$$

where $\mathbf{x}_{ij}$ is a $p \times 1$ vector for jth individual in ith family measured on p covariates, β is a $p \times 1$ vector of covariates, and residual errors ϵ_{ij} across all observations are assumed to be identically and independently distributed (iid) having normal distribution with mean zero and

variance σ_R^2. Note, observations y_{ij} within the same family are most likely correlated, but multiple regression model M_0 does not account for this. Model M_1 will account for this correlation by introducing a random intercept u_i for every family:

$$\begin{aligned} y_{ij} &= \mathbf{x}_{ij}^T\beta + u_i + \epsilon_{ij} \\ \epsilon_{ij} &\overset{iid}{\sim} N(0, \sigma_R^2), \end{aligned} \tag{5.2}$$

where u_i is normally distributed with mean zero and variance σ_u^2, definitions of $\mathbf{x}_{ij}$, β and ϵ_{ij} are the same as in (5.1), random terms are mutually independent.

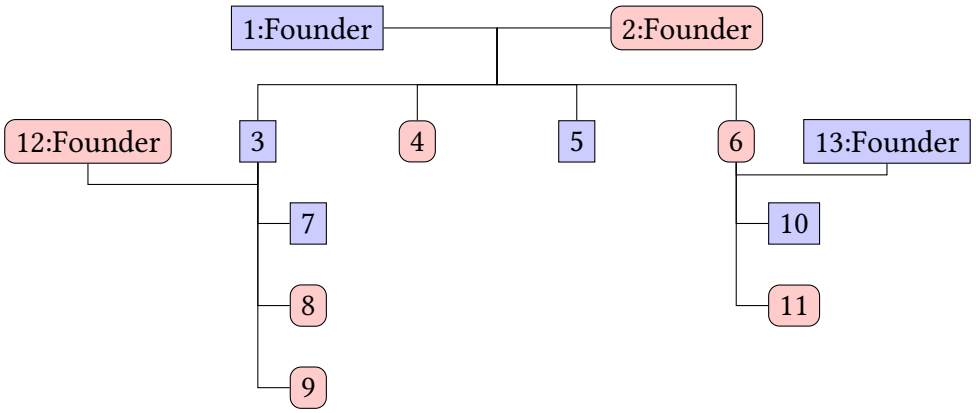
Note, model M_1 does not disentangle the genetic and shared environmental variation. Since one of the goal is to estimate the variance contribution in MCS and PCS due to various factors, therefore model M_2 will assume the genetic correlation between family members that is due to additive genetic effects of alleles (with no dominant and epistatic effects). By assuming all genetic information is in founders, and consequently imposing the fractional relatedness effect between founders and other members of the family, model M_2 introduces the random slopes υ_i for set of founders m_i in family i and can be formulated:

$$\begin{aligned} y_{ij} &= \mathbf{x}_{ij}^T\beta + \mathbf{F}_{ij}^T\upsilon_i + \epsilon_{ij} \\ \epsilon_{ij} &\overset{iid}{\sim} N(0, \sigma_R^2), \end{aligned} \tag{5.3}$$

where definitions of $\mathbf{x}_{ij}$, β and ϵ_{ij} are the same as in (5.1); $\mathbf{F}_{ij}$ is $m_i \times 1$ vector of founders for individual j in family i with $k = 1, \ldots, m_i$, F_{ijk} is a fractional relatedness of individual j to founder k in family i with $\sum_{k=1}^{m_i} F_{ijk} = 1$; υ_i is $m_i \times 1$ vector of random slopes for founders in family i where $\upsilon_i = (\upsilon_{i1}, \ldots \upsilon_{im_i})$, $\upsilon_{ik} \overset{iid}{\sim} N(0, \sigma_f^2)$. We assume independent structure between random terms υ_{ik} $\forall k$, having equal variances σ_f^2 for all founders.

An example of the family i consisting of 13 members with respective fractional relatedness matrix $\mathbf{F}_i$ is demonstrated hereafter. For example, member 3 has 1/2 fractional relatedness effect with founders F1 and F2, and does not have fractional relatedness effect with founders F12 and F13. Similarly, member 7 has 1/4 relatedness effect with founders F1 and F2, 1/2 relatedness effect with founder F12 and does not have

relatedness effect with founder F13.



$$\mathbf{F}_i = \left(\begin{array}{c|cccc} & F1 & F2 & F12 & F13 \\ \hline 1 & 1 & 0 & 0 & 0 \\ 2 & 0 & 1 & 0 & 0 \\ 3 & 1/2 & 1/2 & 0 & 0 \\ 4 & 1/2 & 1/2 & 0 & 0 \\ 5 & 1/2 & 1/2 & 0 & 0 \\ 6 & 1/2 & 1/2 & 0 & 0 \\ 7 & 1/4 & 1/4 & 1/2 & 0 \\ 8 & 1/4 & 1/4 & 1/2 & 0 \\ 9 & 1/4 & 1/4 & 1/2 & 0 \\ 10 & 1/4 & 1/4 & 0 & 1/2 \\ 11 & 1/4 & 1/4 & 0 & 1/2 \\ 12 & 0 & 0 & 1 & 0 \\ 13 & 0 & 0 & 0 & 1 \end{array}\right)$$

Model M_3 is a combination of models M_1 and M_2, and can be written:

$$\begin{aligned} y_{ij} &= \mathbf{x}_{ij}^T\beta + u_i + \mathbf{F}_{ij}^T\upsilon_i + \epsilon_{ij} \\ \epsilon_{ij} &\overset{iid}{\sim} N(0, \sigma_R^2), \end{aligned} \tag{5.4}$$

where definitions and assumptions used in models M_1 and M_2 remain true for this model. Variance components σ_u^2, σ_f^2, σ_R^2 are due to shared environmental, genetic and unique factors, respectively.

5.2.4 Model selection and inference for fixed effects

To select the best model we compared Akaike information criterion (AIC) (Akaike, 1974) and Bayesian information criterion (BIC) (Schwarz et al., 1978) across four models. We define AIC and BIC for these models as:

$$\begin{aligned} AIC &= -\ell(\theta|\mathbf{y}) + 2n_{par} \\ BIC &= -\ell(\theta|\mathbf{y}) + n_{par}\ln(N), \end{aligned} \tag{5.5}$$

where $\ell(\cdot)$ is the log-likelihood function for the estimated model with θ be a vector of parameters, n_{par} denotes the number of parameters in the model, and N is the total number of observations used to fit the model. Model with the smallest AIC is preferred, likewise for BIC.

The overall significance of each covariate is tested using conditional F-test (Pinheiro and Bates, 2009, Chapter 2). In conditional F-test, the fixed effects are tested sequentially in the order they enter the model. The significance of each covariate coefficient is tested in the presence of the covariates listed in the previous model.

Let L be the number of fixed effects coefficients $\beta' = (\beta_1, \ldots, \beta_L)$, where $l = 1, \ldots, L$. Note, some of the fixed effects can be categorical variables, leading to difference between L and p. For individual coefficient β_l, the confidence intervals are constructed based on conditional t-tests. Each fixed effect coefficient can be tested conditionally on all other fixed effects in the model (Pinheiro and Bates, 2009, pp. 92-96). The approximate $100\%(1-\alpha)$ confidence limits on the β_l are computed as:

$$\hat{\beta}_l \pm t_{df_l}(1-\alpha/2)\sqrt{\widehat{var(\hat{\beta})}_{ll}}, \tag{5.6}$$

where $\hat{\beta}_l$ is an estimate of l^{th} fixed effect, $t_{df_l}(q)$ denotes the q^{th}-quantile of a t-distribution with df_l degrees of freedom and $\widehat{var(\hat{\beta})}_{ll}$ is an estimate of the variance of $\hat{\beta}_l$. Clearly, $\widehat{var(\hat{\beta}')}$ is the variance-covariance matrix of the vector $\hat{\beta}'$ of fixed effects estimates. More on determination of degrees of freedom for our models is in Section 5.3.3.

5.2.5 Confidence interval for heritability

Broad heritability, H^2 is defined as the proportion of variance due to all genetic components in the total phenotypic variance (Sham, 1998, p.212). The genetic variance consists of the following three components: variance due to additive genetic effects, variance due to interaction between alleles in the same locus (dominance genetic effects), and variance due to interaction between alleles at different loci (epistatic

genetic effects). Narrow heritability, h^2 is defined as the proportion of variance due to additive genetic component in the total phenotypic variance. In the context of our models, M_1 leads to "broad-type of heritability", H^2, M_2 leads to "narrow-type of heritability", h^2, and M_3 to both of them. Formulas of heritabilities are shown below:

$$H^2 = \frac{\sigma_u^2}{\sigma_u^2 + \sigma_R^2} \qquad\qquad h^2 = \frac{\sigma_f^2}{\sigma_f^2 + \sigma_R^2}. \tag{5.7}$$

For convenience of the notation, we outline the beta-approach on the example of H^2, though it can be similarly applied to h^2. The distribution of the heritability estimator H^2 is approximated with a beta distribution, $\hat{H}^2 \sim \text{Beta}(a, b)$ with parameters $a > 0$ and $b > 0$. If $\hat{H}^2$ is an estimate of the mean and $\hat{\tau}^2_{\hat{H}^2}$ is an estimate of the variance of $\hat{H}^2$, the method of moment estimates for a and b are:

$$\begin{aligned} \hat{a} &= \frac{\hat{H}^2[\hat{H}^2(1-\hat{H}^2) - \hat{\tau}^2_{\hat{H}^2}]}{\hat{\tau}^2_{\hat{H}^2}} \\ \hat{b} &= \frac{(1-\hat{H}^2)[\hat{H}^2(1-\hat{H}^2) - \hat{\tau}^2_{\hat{H}^2}]}{\hat{\tau}^2_{\hat{H}^2}}. \end{aligned} \tag{5.8}$$

The first-order Taylor expansion is used to approximate the variance of $\hat{H}^2$:

$$\hat{\tau}^2_{\hat{H}^2} = \frac{\hat{\sigma}_R^4}{(\hat{\sigma}_u^2 + \hat{\sigma}_R^2)^4}\hat{\tau}^2_{\hat{\sigma}_u^2} + \frac{\hat{\sigma}_u^4}{(\hat{\sigma}_u^2 + \hat{\sigma}_R^2)^4}\hat{\tau}^2_{\hat{\sigma}_R^2} - \frac{2\hat{\sigma}_u^2\hat{\sigma}_R^2}{(\hat{\sigma}_u^2 + \hat{\sigma}_R^2)^4}\hat{\tau}_{\hat{\sigma}_u^2,\hat{\sigma}_R^2}, \tag{5.9}$$

with $\hat{\tau}^2_{\hat{\sigma}_u^2}$ and $\hat{\tau}^2_{\hat{\sigma}_R^2}$ be the estimated variance of estimators $\hat{\sigma}_u^2$ and $\hat{\sigma}_R^2$ respectively, and $\hat{\tau}_{\hat{\sigma}_u^2\hat{\sigma}_R^2}$ be the estimated covariance of the estimators $\hat{\sigma}_u^2$ and $\hat{\sigma}_R^2$. The approximate $100\%(1-\alpha)$ confidence interval on the H^2 in (5.7) is then given by the lower and upper confidence limits as:

$$\begin{aligned} LCL_{\hat{H}^2} &= B^{-1}_{\hat{a},\hat{b}}(\alpha/2) \\ UCL_{\hat{H}^2} &= B^{-1}_{\hat{a},\hat{b}}(1-\alpha/2), \end{aligned} \tag{5.10}$$

with $B^{-1}_{\hat{a},\hat{b}}(q)$ be the q^{th}-quantile of the Beta(a, b) distribution. Detailed description of the beta-approach is given by Demetrashvili et al. (2014).

5.3 Results

Analysis is conducted with R, version 3.0.1. Variance components models are fitted using lme function of package nlme with maximum likelihood estimation method. All results below are presented for two-sided 95% confidence intervals.

A subsample of the baseline LifeLines cohort was used, consisting of 95433 participants. Among all participants, 57.6% were recruited via the general practitioner, 29.6% via the family member and 12.8% via self-registration. Considering the assumptions given in section 5.2.1 we formed extended families. Altogether, 61933 families are constructed. The number of families with a number of family members are summarized in Table 5.1. Clearly, the largest family has 14 members. There are 42100 singletons, 12106 families have two members, etc. About 32% of all reconstructed families have at least two family members in LifeLines, i.e. (61933-42100)/61933. About 55% of all participants have at least one family member in LifeLines, i.e. (95433-42100)/95433. Note, we did not see more self-registrants (i.e. volunteers) among singletons than in families with two or more members (results now presented here). We omitted 2541 (2.7%) observations for both, MCS and PCS.

Table 5.1: Distribution of families by family sizes of all 95433 participants

family size	1	2	3	4	5	6	7	8	9	10	11	14
number of families	42100	12106	4088	2199	895	339	139	43	12	8	3	1

33 observations were missing for BMI, but they were among missing observations for MCS and PCS. No missing values were detected for gender or age. Finally, 92892 observations were analyzed. The distribution of both outcomes, MCS and PCS are slightly left-skewed (the long tail is on the left hand side). The median (25th, 75th percentile) MCS and PCS were 52.9 (48.1, 56.1) and 54.5 (50.3, 56.8), respectively. We re-analyzed descriptive statistics shown in Table 5.1 for 92892 participants and presented the results in Table 5.2. Number of families reduced from 61933 to 60765. As in above results, about 32% reconstructed families have at least two family members in LifeLines, i.e. (60765-41461)/60765 and about 55% participants have at least one family member in LifeLines, i.e. (92892-41461)/92892.

Table 5.2: Distribution of families by family sizes of all 92892 participants

family size	1	2	3	4	5	6	7	8	9	10	11	13
number of families	41461	11915	4022	2059	825	298	128	39	8	6	3	1

5.3.1 Descriptive statistics of covariates

BMI is calculated by dividing a person's weight measurement (in kilograms) by the square of their height (in meters) and subsequently categorized into six categories: underweight (< 18.5) kg/m^2, normal weight $(18.5 - 24.9)$ kg/m^2, overweight $(25.0 - 29.9)$ kg/m^2, class I obese $(30.0 - 34.9)$ kg/m^2, class II obese $(35.0 - 39.9)$ kg/m^2, class III obese (> 40) kg/m^2 (WHO, 1995). Out of 92892 observations, 671 (0.7%) are underweight, 40783 (43.9%) are normal, 36939 (40%) are overweight, 10895 (11.7%) are obese I, 2688 (2.8%) are obese II, and 916 (0.9%) are obese III.

We calculated the proxy age by subtracting the year of birth from 2010 (2010 is proxy year taken from recruitment period 2006-2013). All subjects are 16 years and older. Distribution of age is approximately normal, with average age 44. Out of 92892 observations, 38287 (41$\%$) are men and the rest are women. Same proportions hold for males and females when all 95433 observations were summarized.

To visualize the population parameters, we categorized age in six groups (with increment of 10 years). In Table 5.3, for every age group we show the number of individuals by BMI category, with marginal percentages across age groups. In Table 5.4, for every gender we show the number of males (M) and females (F) by BMI category, with marginal percentages across genders.

Table 5.3: BMI categories by age groups with marginal total across age groups

age	underweight	normal	overweight	obese I	obese II	obese III	total
≤ 29	282 (2.4%)	7477 (63%)	3048 (25.7%)	774 (6.6%)	191 (1.6%)	87 (0.7%)	11859
30-39	156 (0.8%)	9555 (48.9%)	7064 (36.2%)	1968 (10.1%)	572 (3%)	198 (1%)	19513
40-49	151 (0.5%)	14141 (42.0%)	13682 (40.6%)	4209 (12.5%)	1127 (3.3%)	386 (1.1%)	33696
50-59	51 (0.3%)	6166 (37.4%)	7456 (45.1%)	2206 (13.4%)	461 (2.8%)	161 (1%)	16501
60-69	26 (0.3%)	2768 (30.7%)	4453 (49.5%)	1406 (15.7%)	281 (3.1%)	63 (0.7%)	8997
≥ 70	5 (0.2%)	676 (29.1%)	1236 (53.1%)	332 (14.3%)	56 (2.4%)	21 (0.9%)	2326

Table 5.4: BMI categories by gender with marginal total across genders

age	underweight	normal	overweight	obese I	obese II	obese III	total
M	126 (0.3%)	13959 (36.5%)	18673 (48.8%)	4619 (12.0%)	727 (1.9%)	183 (0.5%)	38287
F	545 (1.0%)	26824 (49.1%)	18266 (33.5%)	6276 (11.5%)	1961 (3.6%)	733 (1.3%)	54605

5.3.2 Model selection, variance components and heritability

In the analysis of all models we used 92892 observations with 60765 constructed families. BMI is treated as a categorical variable with 6 levels where normal is a reference category. Age and gender are included in all models. Age is treated as a continuous variable. Gender is a categorical variable with male be a reference category. Model M_0 is a multiple regression model with BMI, age and gender. Models M_1, M_2 and M_3 are the variance components models. M_1 models the random component of the family. M_2 models the random components of the founders. M_3 models both, the random components of the family and founders.

Table 5.5: Estimates of variance components, heritability and its confidence interval for outcomes MCS and PCS

Outcome	Model	Estimator	Estimate	Heritability	$\widehat{LCL}$	$\widehat{UCL}$	AIC	BIC
MCS	M_0	$\hat{\sigma}^2_R$	72.795				661920	662005
	M_1	$\hat{\sigma}^2_u$	12.752	0.174	0.165	0.184		
		$\hat{\sigma}^2_R$	60.391				660959	661053
	M_2	$\hat{\sigma}^2_f$	11.436	0.155	0.145	0.165		
		$\hat{\sigma}^2_R$	62.497				661693	661787
	M_3	$\hat{\sigma}^2_u$	12.75	0.174	0.165	0.184		
		$\hat{\sigma}^2_f$	6.9×10^{-6}	1.27×10^{-7}	0	1		
		$\hat{\sigma}^2_R$	60.39				660961	661065
PCS	M_0	$\hat{\sigma}^2_R$	47.486				622242	622327
	M_1	$\hat{\sigma}^2_u$	3.473	0.073	0.062	0.085		
		$\hat{\sigma}^2_R$	44.034				622015	622109
	M_2	$\hat{\sigma}^2_f$	8.412	0.174	0.164	0.184		
		$\hat{\sigma}^2_R$	39.919				621960	622054
	M_3	$\hat{\sigma}^2_u$	1.860	0.039	0.028	0.051		
		$\hat{\sigma}^2_f$	6.090	0.127	0.116	0.137		
		$\hat{\sigma}^2_R$	40.159				621919	622023

We used AIC and BIC for model selection. BIC consistently chooses

the parsimonious model (i.e. with fewest parameters) for large sample size, while AIC will not necessarily choose the most parsimonious model and may overfit (Claeskens and Hjort, 2008, Chapter 4). Thus, using AIC and BIC, model M_1 provides the best fit for MCS, and M_3 for PCS. Since the best model for MCS is modelling the shared environmental factors, therefore heritability results in Table 5.5 imply that 16-18% variation in MCS is determined by variation in shared environmental factors. Regarding the best model M_3 for PCS, it is modelling the shared environmental as well as the genetic contribution, leading to following interpretation: 12-14% variation in PCS is determined by variation in genetics and 3-5% by variation in shared environment. Heritabilities with respect to specific founders can also be calculated (further work).

5.3.3 Estimates of fixed effects

The result of F-test is presented in Table 5.6, namely the numerator and denominator degrees of freedom[I] of F-value, the F-value itself and respective p-value. Obviously, BMI, age and gender have statistically significant effect on MCS, as well as on PCS. The results for individual effects are presented on Figures 5.1 and 5.2 and in Table 5.7.

Table 5.6: Conditional F-tests for BMI, age and gender of selected models

Model	Term	Numerator df	Denominator df	F-value	p-value
MCS: M_1	Intercept	1	60764	2798896.1	$< .0001$
	BMI	5	32120	73.0	$< .0001$
	Gender	1	32120	1138.5	$< .0001$
	Age	1	32120	1230.3	$< .0001$
PCS: M_3	Intercept	1	60764	5015779	$< .0001$
	BMI	5	32120	663	$< .0001$
	Gender	1	32120	462	$< .0001$
	Age	1	32120	1882	$< .0001$

Figures 5.1 and 5.2 show the effect sizes of BMI (middle line) with respect to reference category surrounded by confidence intervals (outer lines) of these effects. Plain lines are used for selected models of MCS

[I]The denominator degree of freedom for intercept is 60764, which is calculated by subtracting one (intercept of fixed effects) from the number of families. The denominator degrees of freedom for slopes are 32120, which are calculated by subtracting the number of families and the number of slopes of fixed effects from the number of observations (i.e. 92892-60765-7). These degrees of freedom are also used in t-test.

and PCS. Dashed lines are used for three other models. Obviously, the effects of BMI on MCS and PCS of HRQofL match very closely across four models (lines overlap) and this is true for all categories of BMI. Confidence intervals also match very closely. This implies that the BMI effects do not change with and without accounting for relatedness in a family.

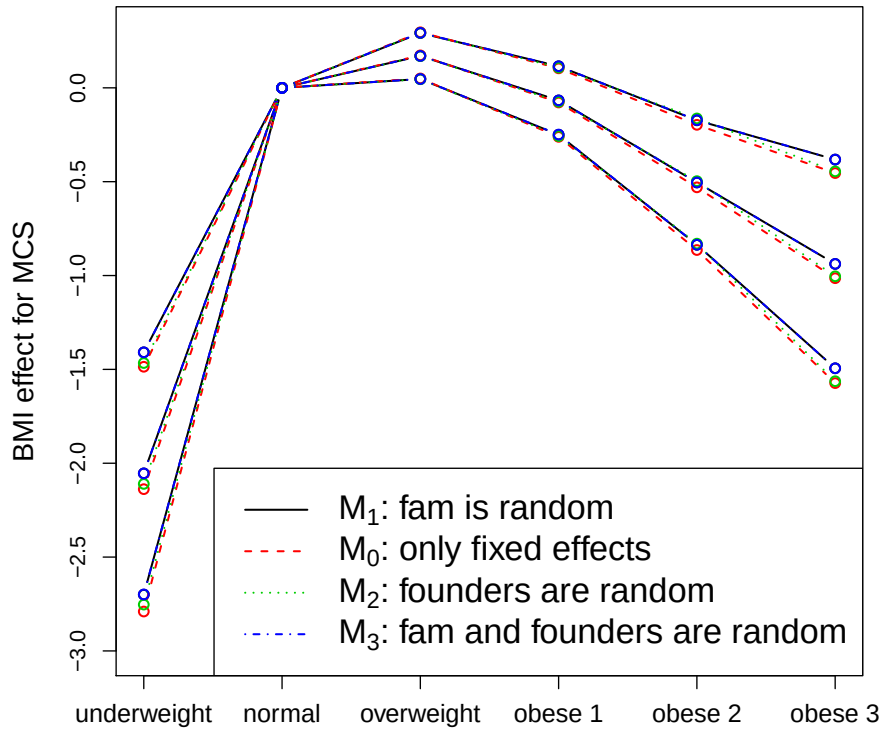


Figure 5.1: BMI effects surrounded by confidence intervals for MCS (normal is reference)

In Table 5.7 we present the coefficients for fixed effects with measures of uncertainty, namely standard error, lower and upper confidence limits. Reults show that each additional year of age is associated with a 0.081 unit increase (0.1% of maximum observed value) in MCS and decrease by about the same amount in PCS, on average, holding BMI and gender constant. Female have lower MCS, by approximately 1.865 units (2.5% of maximum observed value) and lower PCS, by approximately 1.008 units (1.4%), on average, holding BMI and age constant. Interestingly, the MCS increases for overweight people com-

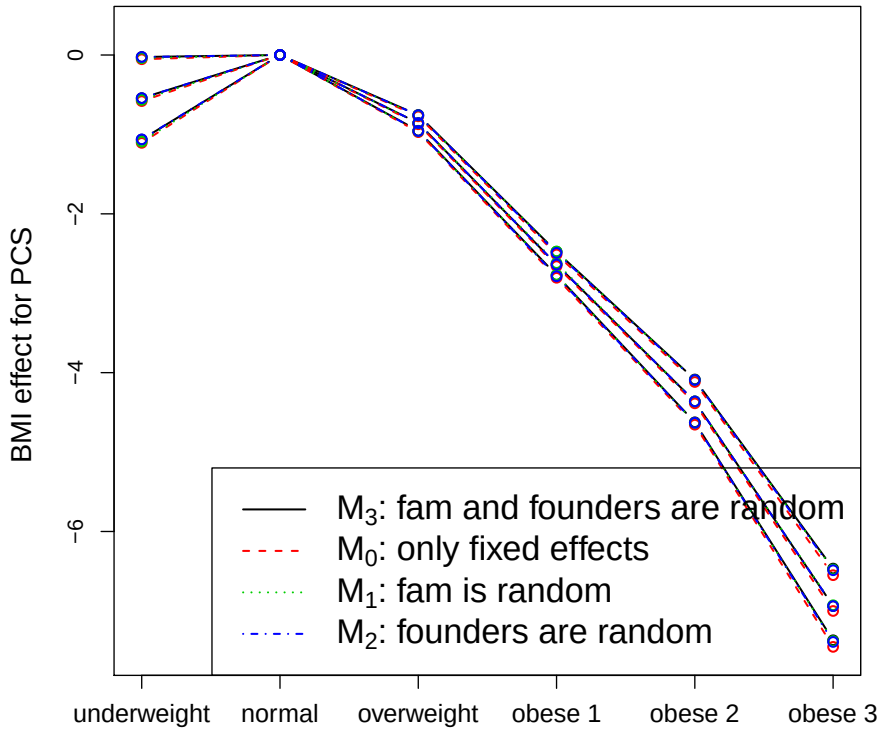


Figure 5.2: BMI effects surrounded by confidence intervals for PCS (normal is reference)

pared to normal category. MCS drops for all other categories compared to normal category and the drop is most prominent for underweight individuals. The PCS decreases for all categories of BMI compared to normal category and the decreasing trend of PCS is steep with increasing BMI.

5.4 Discussion

In this study we aimed to answer whether relatedness in a family must be accounted for when the effect estimates of risk factors are of interest. The answer on this question is of particular importance for the researchers who are analyzing the LifeLines data and may be for researchers from other studies. From our study it is clear that the effects of BMI on MCS and PCS of HRQoL scores do not change with or without accounting for family structure. This conclusion matches with conclusion of others (McArdle et al., 2007). McArdle et al. (2007)

Table 5.7: Estimates of coefficients for BMI, age and gender of selected models

Model	Parameter	Estimate	Std.E	$\widehat{LCL}$	$\widehat{UCL}$
MCS: M_1	Intercept	48.075	0.111	47.857	48.292
	BMI (underweight)	-2.054	0.329	-2.699	-1.409
	BMI (overweight)	0.170	0.063	0.047	0.292
	BMI (obese 1)	-0.067	0.093	-0.249	0.115
	BMI (obese 2)	-0.504	0.169	-0.836	-0.172
	BMI (obese 3)	-0.938	0.284	-1.494	-0.382
	Gender	-1.865	0.056	-1.974	-1.756
	Age	0.081	0.002	0.076	0.085
PCS: M_3	Intercept	57.430	0.089	57.254	57.605
	BMI (underweight)	-0.545	0.265	-1.065	-0.025
	BMI (overweight)	-0.854	0.051	-0.954	-0.755
	BMI (obese 1)	-2.625	0.075	-2.772	-2.477
	BMI (obese 2)	-4.356	0.138	-4.625	-4.086
	BMI (obese 3)	-6.918	0.230	-7.370	-6.467
	Gender	-1.008	0.046	-1.099	-0.917
	Age	-0.080	0.002	-0.084	-0.077

conducted simulation study with the objective to compare the performance of association analysis of family based designs that account for and ignore family structure in assessment of the phenotype-genotype association. They concluded that effect size estimates and power are not significantly affected by ignoring family structure. Though, type 1 error rates increase when family structure is ignored. Note, the study of McArdle et al. (2007) was a simulation study with specific assumptions on family structure. In this work we studied real data and did not assume any a priori family inheritance structure. Thus, we think that the main strength of our study is the use of LifeLines data which makes possible to model the relatedness in more complex families than other studies can. Consequently, our results are practically more relevant.

We made an assumption in our study that founders are unrelated, but LifeLines may not have complete information.

MCS and PCS maybe genetically correlated meaning that there is genetic overlap between these two traits (same set of genes may regulate these traits). If interest lies in separation of genetic and environmental contributions simultaneously in MCS and PCS, then bivariate models could be used, likewise others (Yip et al., 2008, Lichtenstein et al., 2009) who modeled schizophrenia and bipolar disorder using

multivariate generalized linear mixed model.

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